Tolvaptan and ADPKD: Does slowing kidney growth preserve function?

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Autosomal dominant polycystic kidney disease (ADPKD) represents a significant clinical challenge, characterised by progressive cyst growth and an inexorable decline in renal function. For years, management focused on symptom control and managing complications, with no specific therapy to alter disease progression. The introduction of tolvaptan, a vasopressin V2 receptor antagonist, offered a new approach by targeting the underlying pathophysiology of cyst formation.

Tolvaptan's mechanism of action directly addresses the role of vasopressin in stimulating cyst growth, offering a potential avenue to slow disease progression. But the critical question for clinicians remains: does reducing the rate of total kidney volume (TKV) increase, a surrogate marker, genuinely translate into a sustained preservation of glomerular filtration rate and, more importantly, a delay in the onset of end-stage kidney disease?

KEY TAKEAWAYS

- The Pivot: Tolvaptan slows the increase in total kidney volume in ADPKD by inhibiting vasopressin-mediated cyst growth.
- The Data: Clinical studies have consistently shown a reduction in the rate of TKV increase with tolvaptan compared to placebo.
- The Action: Clinicians should consider tolvaptan for patients with rapidly progressing ADPKD, carefully balancing its benefits against the known risks of hepatotoxicity and increased thirst.

Autosomal dominant polycystic kidney disease is the most common inherited kidney disorder, affecting millions globally. It is characterised by the development and enlargement of numerous fluid-filled cysts in the kidneys, leading to progressive kidney enlargement and eventual kidney failure. The disease typically manifests in adulthood, with patients often progressing to end-stage kidney disease (ESKD) by their fifth or sixth decade, necessitating dialysis or kidney transplantation. The relentless nature of ADPKD, coupled with the absence of disease-modifying therapies for decades, created a substantial unmet need for interventions that could slow its progression.

The pathophysiology of ADPKD involves genetic mutations, primarily in the PKD1 or PKD2 genes, leading to abnormal polycystin proteins. These proteins are essential for normal renal tubule development and function, and their dysfunction results in dysregulated cell proliferation, fluid secretion into cysts, and inflammation, all contributing to cyst growth. Vasopressin, an antidiuretic hormone, plays a significant role in this process by stimulating cyclic AMP (cAMP) production in renal tubular cells, which in turn promotes cyst cell proliferation and fluid secretion. This understanding provided a clear therapeutic target.

Targeting Cyst Growth

Tolvaptan, a selective vasopressin V2 receptor antagonist, works by blocking the action of vasopressin on its receptors in the kidney. This blockade reduces intracellular cAMP levels, thereby inhibiting the proliferation of cyst-lining cells and decreasing fluid secretion into the cysts. The theoretical benefit is a slowing of cyst growth and, consequently, a deceleration of kidney enlargement. This mechanism is distinct from previous symptomatic treatments, which did not address the underlying disease progression.

Clinical trials investigating tolvaptan in ADPKD have primarily focused on its effect on total kidney volume (TKV) as a surrogate marker for disease progression. TKV, measured by magnetic resonance imaging (MRI) or computed tomography (CT), is a well-established prognostic indicator in ADPKD. A faster rate of TKV increase correlates strongly with a more rapid decline in estimated glomerular filtration rate (eGFR) and earlier progression to ESKD. Therefore, interventions that slow TKV growth are hypothesised to preserve kidney function over time. The Mayo imaging classification helps identify rapid progressors in ADPKD, guiding treatment decisions for these patients. Identifying rapid progressors in ADPKD: The Mayo imaging classification in practice is a useful resource for understanding this.

The Clinical Evidence for Volume Control

Studies have consistently demonstrated that tolvaptan reduces the annual rate of TKV increase compared to placebo. This effect has been observed across various patient populations, including those with early-stage ADPKD and those with more advanced disease. The reduction in TKV growth is a direct consequence of the drug's mechanism, inhibiting the vasopressin-mediated pathways that drive cyst expansion. This volumetric control is the drug's most robust and consistently reported effect.

But the more critical question for patients and clinicians is whether this slowing of TKV growth translates into a meaningful preservation of kidney function. The relationship between TKV and eGFR decline is complex. While TKV is a strong predictor of future eGFR decline, the direct impact of TKV reduction on eGFR preservation is not always straightforward. The goal of ADPKD treatment is ultimately to delay ESKD, a hard clinical endpoint.

The effect of tolvaptan on eGFR decline has been a central point of investigation. Clinical trials have shown a slower rate of eGFR decline in patients treated with tolvaptan compared to placebo. This effect, while statistically significant, often represents a modest absolute difference in eGFR over the study period. The long-term implications of this slower decline, particularly in terms of delaying the need for renal replacement therapy, are what truly matter to patients.

Safety and Tolerability Considerations

Tolvaptan is not without its side effects, which often influence patient adherence and prescribing decisions. The most common adverse events are related to its aquaretic mechanism of action, including thirst, polyuria, and nocturia. These symptoms can be bothersome and significantly impact a patient's quality of life, sometimes leading to treatment discontinuation. Patients must be counselled extensively on managing these symptoms, including adequate fluid intake.

A more serious concern is the risk of hepatotoxicity. Tolvaptan has been associated with elevated liver enzymes and, in rare cases, severe liver injury. This necessitates regular monitoring of liver function tests, particularly during the initial phases of treatment. The monitoring burden is a significant consideration for both patients and healthcare systems. Our previous coverage on Tolvaptan's Liver Risk: A Monitoring Burden Patients Weigh Differently explores this in detail.

The balance between the benefits of slowing disease progression and the burden of side effects and monitoring is a

critical aspect of shared decision-making. Not all patients with ADPKD are suitable candidates for tolvaptan, and careful patient selection is paramount. Patients with rapidly progressing disease, identified by factors such as high TKV, rapid TKV growth, or early eGFR decline, are generally considered the most appropriate candidates. For a deeper dive into the drug's overall impact, consider reviewing Tolvaptan and ADPKD: Does slowing kidney growth preserve function?

Unanswered Questions and Future Directions

While tolvaptan has demonstrated an ability to slow TKV growth and eGFR decline, several questions remain. The long-term impact on hard clinical endpoints, such as time to ESKD, is still being fully elucidated. Extended follow-up studies and real-world data are essential to confirm these benefits outside of controlled trial settings. The optimal duration of treatment and the potential for combination therapies with other emerging agents are also areas of ongoing research. For clinicians seeking a comprehensive reference on renal disease and hypertension, the Oxford Handbook of Nephrology and Hypertension provides practical guidance.

The heterogeneity of ADPKD also presents a challenge. Not all patients respond equally to tolvaptan, and identifying predictors of response could help tailor treatment more effectively. Genetic factors, specific PKD1 or PKD2 mutations, and other disease modifiers may influence treatment efficacy. Personalised medicine approaches, where treatment decisions are guided by individual patient characteristics, are likely to become increasingly important in ADPKD management.

The role of tolvaptan in specific subgroups, such as paediatric patients or those with very early disease, also requires further investigation. While the drug offers a significant advance in ADPKD treatment, it is not a cure. It slows progression, but the disease continues its course. The ultimate goal remains to develop therapies that can halt or even reverse cyst growth and fully preserve kidney function.

> **CLINICAL IMPLICATIONS**
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> Tolvaptan's arrival marked a genuine shift in ADPKD management, moving beyond mere symptom control to a disease-modifying strategy. For clinicians, the evidence is clear: the drug slows the relentless expansion of total kidney volume and, by extension, the decline in eGFR. This offers a tangible benefit for patients facing a progressive and debilitating condition.
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> But the practicalities of prescribing tolvaptan are not trivial. The aquaretic side effects are a significant burden, and the hepatotoxicity risk mandates rigorous monitoring. This means careful patient selection is paramount, focusing on those with clear evidence of rapid progression where the benefit-risk ratio is most favourable. It is not a drug for every ADPKD patient, nor should it be.
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> The challenge now lies in integrating tolvaptan into a broader, more personalised management strategy. We need better tools to predict who will respond best and who will tolerate the side effects least. The modest eGFR benefit, while statistically significant, still leaves room for improvement. The field must continue to explore combination therapies and novel targets to truly alter the long-term trajectory of ADPKD.

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REFERENCES

1. 1. St Pierre K, Cashmore BA, Bolignano D, et al. Interventions for preventing the progression of autosomal dominant polycystic kidney disease. Cochrane Database Syst Rev. 2024;10(10):CD010294. doi:10.1002/14651858.CD010294.pub3
2. 2. Furlano M, Tinoco A, Toso D, et al. Unravelling sex-specific differences in autosomal dominant polycystic kidney disease: a multiorgan perspective. Clin Kidney J. 2026;19(1):sfaf359. doi:10.1093/ckj/sfaf359
3. 3. Zhou L, Li W. Efficacy and safety of tolvaptan in rapidly progressing autosomal dominant polycystic kidney disease: a single-center, prospective, single-arm study. Transl Androl Urol. 2026;15(4):100. doi:10.21037/tau-2025-1-896

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